Laboratory-Associated Zika Virus, United States

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Susan Hills. She's a medical epidemiologist at CDC in Fort Collins, Colorado. We'll be discussing cases of laboratory-associated Zika virus disease in the United States.

Welcome, Dr. Hills

[Susan Hills] Thank you very much for having me.

[Sarah Gregory] So what is Zika virus? By now most everyone has heard of it but I'm guessing many people don't actually know what it is or what causes it.

[Susan Hills] So, Zika virus is one of the viruses in the *Flaviviridae* family, and other viruses in this family that people are probably more familiar with are West Nile virus that occurs in the United States, and then there are viruses like yellow fever, Japanese encephalitis, and dengue that occur in other parts of the world. And these are all flaviviruses like Zika virus. And then Zika virus is an arbovirus, or arthropodborne virus, and that just refers to the fact that the main way this virus is transmitted is by an arthropod—in this case, by mosquitoes.

[Sarah Gregory] When and where was it first discovered?

[Susan Hills] So, Zika virus was first isolated in 1947 from a monkey in the Zika Forest of Uganda. Researchers at the time were actually working on a yellow fever study in the Zika Forest, and they were investigating what mosquito spread the yellow fever virus between monkeys in the forest. But during that study, one monkey they were monitoring developed a fever, and when they bled the monkey they found it had a new virus that hadn't been identified before. And so because it was in the Zika Forest they named it Zika virus.

[Sarah Gregory] So, Zika first became a public health emergency of international concern in 2015. What caused it to become an epidemic after being around for so long?

[Susan Hills] So, you're right that up until about 2007, actually, only occasional human disease cases were reported from countries, that was from Africa and from Southeast Asia. In 2007, the first documented Zika virus outbreak was reported in Yap State, Federated States of Micronesia (that's in the Pacific), and then a few years later in 2013, an outbreak began in French Polynesia. And after that the virus actually spread to other Pacific islands. So there had actually been much smaller outbreaks in the Pacific before it appeared in the Americas. It probably got to the Americas being facilitated by global travel—by people traveling from there to the Americas.

The definitive answer as to why it has caused such explosive outbreaks in the last 10 years is not known. It might be related to genetic changes in the virus that resulted in it becoming more transmissible or more virulent, but we really don't have the exact answer to that question.

[Sarah Gregory] So how do people get infected with Zika? You mentioned monkeys, you mentioned mosquitoes. Is it transmissible by all primates? Only mosquitoes? Person to person? What's going on here?

[Susan Hills] So the most common means of transmission is by a mosquito bite, so specifically *Aedes* species mosquitoes. But sexual transmission and transmission from a pregnant mother to her baby (that's called intrauterine transmission), they are also well recognized. In

terms of monkeys, that's a mechanism whereby the virus (at least in Africa) has been determined to spread through mosquitoes between monkey to monkey, but not directly from monkeys to humans.

In addition to…so mosquito bites, sexual transmission, intrauterine transmission, there have been reports of more rare modes of transmission. So, during the birth of the baby (intrapartum transmission is what that is called), through blood transfusion, and breastfeeding, and like in our report, after exposure to the virus in a laboratory.

[Sarah Gregory] If listeners are interested, we did a podcast in 2011 on what was believed to be the first known case of sexually transmitted Zika with, of course, the accompanying article in the journal.

What are the signs and symptoms of Zika?

[Susan Hills] Most people who get sick with Zika virus infection have mild symptoms. So, typically it might be rash, headache, fever, joint pain, red eyes, and muscle pain. It's rare for severe disease to occur, but sometimes it does occur. Very, very occasionally there are hospitalizations and death has been reported.

[Sarah Gregory] Can people not have symptoms and still carry the virus and pass it on to other people?

[Susan Hills] Typically when someone has Zika virus infection, the virus is in the blood for about one or two weeks. And so, during that time if they were bitten by an *Aedes* mosquito, the mosquito could pick up the virus and there's an incubation period in the mosquito, and the mosquito could then pass the virus onto another person that could get sick with Zika. The other possibility is spread through sexual transmission (that we've already mentioned). So, if someone was infected and not aware of it, they could pass the virus onto their sexual partner in this way. In particular, we know that viral RNA (like viral material) can be found for quite some time in semen after a man has been infected with Zika virus. This has sometimes been detected for several months. And so a man who is infected with Zika virus and not aware of it, but who had unprotected sex with his partner, could pass the virus onto his partner in that way. Even though Zika viral material has been found in semen for months, the longest period where sexual transmission from a man to his sexual partner has been documented is just after a month after his illness onset. Nonetheless, because of the risk of transmission in this way, CDC does have recommendations about preventing sexual transmission and they include that if a man has possible Zika virus exposure and his partner is pregnant, they should use condoms or abstain from sex for the duration of the pregnancy. And if a man, or a man and his partner, travel to an area with risk for Zika virus transmission and they're planning to conceive, they should use condoms or abstain from sex for at least 3 months after the possible exposure.

[Sarah Gregory] How is Zika diagnosed?

[Susan Hills] The symptoms of Zika can be very similar to a number of other illnesses, so they include other mosquitoborne illnesses, for example, like dengue and chikungunya. So the only way to diagnose Zika virus infection is with a laboratory test. The most straightforward and accurate test is called a PCR test, or molecular test, and that's the preferred test but it does need to be done within one to two weeks of the onset of symptoms. The test is done on blood and sometimes also on urine. And there are also serologic tests, and they are tests that look for antibodies in the blood or a marker of infection in the blood.

[Sarah Gregory] And is there any treatment for it?

[Susan Hills] We don't have any specific antivirals or other medications that can be used to treat Zika virus disease. Fortunately, most people don't get too sick and typically getting some rest, having plenty of fluids, using over the counter fever or pain medications will be sufficient. If somebody becomes very sick, they might need to be hospitalized for supportive care.

[Sarah Gregory] And what are some of the health problems that can result from getting Zika related to pregnancy?

[Susan Hills] So, the outcome that we're most concerned about with Zika, as you said, is when a pregnant woman becomes infected and that can result in a miscarriage. And though it's not frequent, if the virus does get transmitted to her fetus (her baby), the baby can be infected with Zika virus before it's born and it can sometimes develop microcephaly, which of course is where the baby's head is smaller than expected and development of the brain is affected. And so when the baby is born, they can have a range of problems—developmental delays, seizures, intellectual disability, problems with movement and balance, or things like feeding, hearing, or vision problems. The problems can range from quite mild through to severe, as I'm sure people are aware.

[Sarah Gregory] So during the outbreak in 2015, there seemed to be a lot of microcephaly from that. Tell us about that.

[Susan Hills] Yeah, so we had not recognized this outcome in relation to an arboviral disease previously. There had been occasional case reports, for example with West Nile virus, about a concern about transmission when the baby was in utero. But this was a new phenomenon. And it was actually because of this recognized adverse outcome from Zika virus disease in pregnant women that the disease was recognized as a public health emergency of international concern.

[Sarah Gregory] With the current COVID-19 pandemic over this past year and some, there hasn't been much reporting on Zika. Is it still a concern in the United States? Or is it like flu and colds and other things sort of just laying low?

[Susan Hills] There's currently no local transmission of Zika virus in the continental United States, and in fact there have been no confirmed Zika virus disease cases in United States territories since 2018. In the continental United States, the last time we had transmission was the local transmission that was reported from Florida and Texas in 2016–2017. We do have the mosquito that can carry Zika virus in many places across the U.S., but that doesn't mean that the virus is present. And in fact local and state health departments and mosquito control districts routinely monitor mosquito activity and look for the presence of viruses like Zika. That's the situation in the United States.

Globally, transmission of the virus has likely been interrupted in some areas, but there's probably ongoing low-level transmission in parts of Africa, Asia, and the Americas. As we discussed, symptoms are often mild with Zika virus disease and can be similar to other mosquitoborne diseases. So it can be difficult to track exactly where cases are occurring, especially since the capacity to monitor diseases can be very variable from country to country. As a basic principle, anywhere that has had a previous outbreak of Zika is at risk for future or ongoing spread of the virus. Because of that, CDC does continue to recommend that if you are traveling to a place with a history of Zika, you should take steps to prevent mosquito bites, and that will prevent any transmission of Zika virus but also other mosquitoborne diseases.

[Sarah Gregory] Now we're going to talk about your study a little bit. You looked at four cases of laboratory-associated Zika virus. Why is it important to highlight this?

[Susan Hills] It's important for people working in laboratories to be aware that Zika virus infections have occurred in this setting. Previously, there were only a small number of reports of laboratory-associated Zika virus infections. So our report adds substantially to the information on this topic. Interestingly, one of the earliest reports of human Zika virus infection was possibly laboratory-acquired, and this was back in 1963 when a researcher was working in a laboratory in Uganda with Zika virus strains that he had isolated from mosquitoes. And he developed fever and rash and had a laboratory test, and interestingly he had Zika virus infection. It couldn't definitively be said that he had acquired infection in laboratory rather than through a mosquito bite, but it was thought most likely that it was actually a laboratory-acquired infection.

In about more than 50 years since, only five other laboratory-acquired Zika virus infections have been reported. So the four cases that we report that occurred from 2016 through 2019 not only add substantially to information on the topic, but I think highlight the importance of good laboratory biosafety practices when working with Zika virus—or any other virus, for that matter—in the laboratory. Although Zika virus transmission has decreased substantially in recent years, there still is a lot of Zika virus research ongoing, and exposure and infection are occupational risks for these laboratory and biomedical research workers who are working with the virus, so we've emphasized the importance of strong infection prevention practices to reduce the risk for these workers.

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[Sarah Gregory] So how did you find out about these cases? Were they reported to CDC? And where did they happen?

[Susan Hills] So, Zika virus is a nationally notifiable disease. So that means that any cases of Zika virus disease are required to be reported to the National Notifiable Disease Surveillance System, and that's just a system that monitors a variety of important diseases with the purpose being to be able to better prevent and control those diseases. In addition, clinicians will often seek advice for diagnosis and management in a situation like this where there is a worker who has possibly been exposed to Zika virus and will sometimes contact CDC directly, or they might contact a state health department. And of course we work closely with staff at state health departments. These cases all occurred in workers in research and virology laboratories in various states in the United States.

[Sarah Gregory] How were these laboratory workers exposed? Did they all become exposed in the same way?

[Susan Hills] So among the four cases that we report, two were associated with accidental needlestick injuries—one was a worker inoculating skin cells for research purposes, and the other was recapping a needle after inoculating a mouse with Zika virus. For the other two, we could not definitively determine the means of exposure. For one of the cases, the worker typically worked with large quantities of virus and sometimes this was outside a biosafety

cabinet, and he also couldn't rule out whether he might have rubbed his face with the back of a gloved hand. But as I said, in both of these two latter cases we couldn't specifically pinpoint the actual exposure.

[Sarah Gregory] So lab testing increased greatly during the Zika outbreaks. Did this contribute to more lab incidents?

[Susan Hills] Yeah, I think this had a substantial impact on the increase in infections. Firstly, Zika virus diagnostic testing increased substantially because of the outbreak, so that likely contributed. But in addition, the Zika outbreak generated a lot of additional research being done on Zika virus that was everything from trying to better understand Zika viruses and microcephaly in babies, trying to better understand how a body responds to Zika virus infection, looking at different Zika virus strains from across the world to determine if there had been signs of virulence, and of things like investigating how Zika virus was transmitted sexually. In addition to that, of course there was work on possible treatments and importantly preventive measures—so vaccine research. So that work also increased substantially and of course still continues.

[Sarah Gregory] What safety protocols do you think need to be improved? What more can labs do to protect laboratory personnel who work with Zika or any other pathogen?

[Susan Hills] Typically, I think the safety protocols do exist. So for Zika virus, for example, there are guidelines for appropriate practices, for safety equipment, and facility requirements. Beyond the existing guidelines, I think the other important step is considering individual risk assessments in labs to determine whether there are certain procedures or specimens that might require different approaches or additional steps beyond the general guidelines for a specific pathogen. So for example, in our report, in the situation where somebody was manipulating large quantities of virus or high titer preparations, a risk assessment might perhaps have suggested this might require higher levels of biocontainment, such as additional respiratory protection.

[Sarah Gregory] What are the challenges that labs face in keeping workers safe?

[Susan Hills] I think the main challenge is to ensure safety is kept front and center in any type of lab work. So, ensuring appropriate policies and procedures are established (and of course not just established but implemented), making sure all staff working in laboratories are well-trained and familiar with the safety protocols, ensuring proper personal protective equipment and other safety equipment is available and being used correctly, and ensuring the type of work being performed is appropriate for the laboratory where it's being performed. Laboratorians are often working under time pressures and working long hours, so it's important to ensure that the safety procedures can be implemented as easily as possible and there are not impediments to implementing the recommended measures. I think the other challenge is just for laboratory workers to be aware of the importance of the procedures and practices in preventing infection. And I think our report will be a helpful reminder that getting infected in the laboratory is not just a theoretical issue.

[Sarah Gregory] So if someone working with Zika in a lab thinks they may have been exposed, what steps should they take?

[Susan Hills] So the first step involves the immediate, standard wound management practices or procedures for mucous membrane exposures and then the reporting of event to a supervisor. Any possible exposure does need appropriate evaluation and management by a healthcare

professional. There are no specific medications or treatments that can be used when somebody has possibly been exposed to Zika virus. So unlike exposure to some other pathogens like HIV, there's no specific treatment. But nonetheless, there are important steps to take and that starts with collecting a baseline blood sample. Blood tests for Zika can sometimes be challenging to interpret, so this sample can be collected in case it's needed for comparison with a later sample.

Because the incubation period—and that's the time from exposure to development of symptoms for Zika—it can be anything from a few days to a week or more, and people can be infectious before they show any symptoms. So the person also needs to be careful to take steps to prevent sexual transmission of Zika virus to their sexual partner and to avoid mosquito bites if they live in an area where there's a risk for mosquitoborne transmission of Zika virus, and those measures should be continued until the laboratory testing has ruled out infection. If somebody does develop symptoms consistent with Zika virus disease, and that's within two weeks of the exposure, then blood and urine should be collected and tested for Zika virus infection. If the exposed person doesn't develop any symptoms in that two-week period, a blood sample should be collected at the end of that two-week period, and that's to ensure they haven't been infected without showing symptoms, or asymptomatically infected as we call it.

[Sarah Gregory] Are there factors that affect the likelihood of developing Zika after being exposed to the virus? I mean, can one person get the same exposure and not get it, whereas another person would?

[Susan Hills] There are actually several factors that can affect the likelihood of Zika virus infection, and that's whether it's exposure from a mosquito bite or in a laboratory setting. They include the person's overall health status, the Zika virus strain and its virulence, and genetic factors likely play a role as well. Specifically in a laboratory setting, some of the key factors include the type and severity of any injury or exposure, the route of exposure (so for example, whether it was through a needlestick injury or through inhalational exposure), the viral concentration and dose, and then the immediate management of any recognized exposure. These factors will all contribute to the likelihood of developing Zika virus disease after you've been exposed, and in fact we do know of at least three other occupational exposures to Zika virus where the researchers didn't develop Zika virus infection. Nonetheless, this doesn't lessen the importance of strong infection prevention practices and appropriate management of any accidental exposure that does occur to ensure these laboratory workers are protected from any adverse health outcomes.

[Sarah Gregory] Dr. Hills, tell us about your job at CDC. What interests you about arboviruses?

[Susan Hills] I don't think I can summarize it any better than saying that arboviruses are fascinating. There are about one hundred arboviruses we know about that can cause disease in humans, and then about another one hundred where the relationship to human disease is unknown. So the 20 or so arboviruses that we focus on in our day-to-day work as major human pathogens are really just the tip of the iceberg. I think the question that is always in the back of our minds when we work in arboviral diseases is "What's going to emerge next?" So I've been at CDC for 10 years, and I've seen two arboviruses (chikungunya and Zika virus) emerge from relative obscurity to become major global pathogens. One day it's a relatively unknown arbovirus, and the next it's an epidemic threat. In that same time, our branch has actually discovered two new tickborne viruses, Heartland virus and Bourbon virus. So we really never know what's around the corner. Even with our established pathogens, understanding

transmission dynamics is fascinating. So for example, with West Nile virus in the United States, trying to understand where and why an outbreak might occur and what strategies we can implement to reduce the impact on humans is just very interesting work.

And then finally, we're fortunate that we have several highly effective vaccines for arboviral diseases, including for yellow fever and Japanese encephalitis. Japanese encephalitis, for example, is a devastating disease. Across the world each year it causes about 70,000 cases primarily among children, and about 15,000 children die and another 25,000 are left with disabilities. So, seeing vaccination programs start to be implemented to avoid this very heavy toll from this disease is just really exciting work.

[Sarah Gregory] You're in Fort Collins, Colorado, and the main headquarters for CDC is in Atlanta, where I am. I know dengue is based in Puerto Rico, why are arboviruses studied in Fort Collins?

[Susan Hills] It was related to historically when the division was set up. So previously they would work on various pathogens (one of them was actually plague) that were occurring, and a laboratory was actually set up in Fort Collins in relation to that work that was occurring. And when various other labs and facilities were closed down, there was a decision made to keep this laboratory here in Fort Collins to continue work on both viral and bacterial diseases (vectorborne diseases).

[Sarah Gregory] So tell us a little bit about your life there in Colorado.

[Susan Hills] I think it would be hard not to love living in a city that has more than 240 sunny days a year. We've got a huge number of opportunities for outdoor activities and we have Rocky Mountain National Park only about an hour up the road. So I am even just thankful every day for something as simple as my commute to work, which at least in non-COVID times involved jumping on my bike and then taking a bike path most of the way to the office, and that runs along a creek for most of the way and just listening to the sounds of the creek on the way to work. The main traffic I have to deal with is other bikes on the bike path and the occasional deer or horse that might stray onto the bike path. That truly is a delight.

[Sarah Gregory] Did you say 340 sunny days a year? Did I hear you right?

[Susan Hills] 240.

[Sarah Gregory] Oh my goodness. Well thank you for taking the time to talk with me today, Dr. Hills.

[Susan Hills] It has been my pleasure.

[Sarah Gregory] And thanks for joining me out there. You can read the May 2021 article, Case Series of Laboratory-Associated Zika Virus Disease, United States, 2016–2019, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.